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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/717,708	11/21/2003	Shigeru Ohno	245819US0	8844

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EXAMINER	
LIETO, LOUIS D	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/717,708	OHNO ET AL.	
	Examiner	Art Unit	
	Louis D. Lieto	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 3/29/2005 is acknowledged. Claims 5-8 are pending in the instant application. Applicants canceled claims 1-4, and added claims 5-8. The sections of title 35 U.S.C not included in this office action can be found in a previous office action. An action on the merits follows.

Claim Objections

Claim 5 is objected to because of the following informalities: Claim 5 refers to Genbank Accession No. NM_000358. Gen bank Accession Nos. are not static and can change over time as they are updated. For this reason Applicant may only include SEQ ID Nos. in their claims. Since Applicant has included a reference to SEQ ID NO. 2, the reference to the Genbank No is needlessly duplicative. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The rejection of original claims 1 and 2 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of the cancellation of claims 1 and 2. Applicant's cancellation of the claims filed 3/29/2005 have been fully considered and were found persuasive in overcoming the remaining grounds of rejection.

The rejection of original claims 1,2 and 4 under 36 U.S.C. 112, first paragraph, for scope of enablement, is withdrawn. Applicant's cancellation of the claims filed 3/29/2005 have been fully considered and were found persuasive in overcoming the remaining grounds of rejection.

Claims 5-8 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of suppressing mineralization in periodontal ligament cells isolated from a human and cultured with a human RGD-CAP protein, comprising SEQ ID NO:2, *in vitro*, does not reasonably provide enablement for a method of suppressing mineralization and adhesion in the periodontal ligament of a patient comprising applying a human RGD-CAP protein, comprising SEQ ID NO:2, so that the human RGD-CAP is contacted to periodontal ligament cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. Applicant's addition of claims 5-8 necessitated these new grounds of rejection.

The claims encompass a method of suppressing mineralization and adhesion in the periodontal ligament of a patient comprising any method of application of a human RGD-CAP protein, comprising SEQ ID NO:2, so that the human RGD-CAP is contacted to periodontal ligament cells.

The specification does not provide guidance on any method of administration of full-length human RGD-CAP for suppression of mineralization and adhesion of the periodontal ligament at the time of tooth transplantation. The specification contemplates general approaches to the method of claim 5, however, no working examples are provided. Further, while the specification contemplates applying full-length human GD-CAP to the periodontal ligament or to the dental socket at the time of tooth transplantation; the specification does not specify what is meant by application. The term application includes topical application and subcutaneous injection, amongst others. Both of these application methods would satisfy the limitation of

claim 5 that RGD-CAP is contacted to the periodontal ligament cells. The specification does not provide any working examples demonstrating that any route of application of full-length human GD-CAP can suppress mineralization and adhesion of the periodontal ligament by using full-length human RGD-CAP at the time of tooth transplantation. All of the working examples read on *in vitro* methods of using full-length human RGD-CAP for suppressing ALP activity and bone nodule formation. Further, an effective rout of administration of RGD-CAP in order to suppress mineralization and adhesion of the periodontal ligament at the time of tooth transplantation was not known in the art of record at the time of filing. Finally, the specification fails to teach that effects observed by culturing human periodontal ligament cells with RGD-CAP *in vitro* can be induced by an means of administration by any amount of RGD-CAP to the intact periodontal ligament *in vivo*; and that if such effects were induced that this would lead to a suppression of adhesion. The specification discloses that RGD-CAP binds so tightly to collagen fibers that the protein is resistant to protease and homogenization (Specification pg. 21, lines 1-5). Specifically, boiling of human periodontal ligament in laemmili buffer in 4M urea was required to solubilize the RGD-CAP homogenization (Specification pg. 21, lines 1-5). This raises the concern that RGD-CAP may bind tightly to the collagen fibers of the periodontal ligament, when coated on or injected into it, without inducing any therapeutic effect in the periodontal ligament cells. The lack of any *in vivo* working examples in the specification or the art of record at the time of filing make the induction of any therapeutic effect unpredictable based solely on the *in vitro* examples disclosed.

The specification does not describe the duration of the half-life or the stability of human RGD-CAP or its variants. Further, the specification does not enable any and all methods of

administering full-length human RGD-CAP at the time of tooth transplantation, such as intravenous, topical, or sub dermal application. The specification contemplates that full length human RGD-CAP will be applied to the periodontal ligament or to the dental socket at the time of tooth transplantation, however no dosage of full-length human GD-CAP is specified. The half-life of protein drugs such as tissue type plasmiongen activators (t-PA) can range from 4 minutes for wild-type t-PA to 20 min for a t-PA with a single amino acid substitution. {Verstraete M. (1999) Ann Acad Med Singapore. 28:424-33}. This indicates that proteins that differ by a single amino acid can have vastly different stabilities *in vitro*. There are no working examples that teach that a specific amount or range of amounts of full-length human RGD-CAP, are effective at suppressing mineralization and adhesion of the periodontal ligament by using RGD-CAP at the time of tooth transplantation. Further, the ability of full-length human RGD-CAP to suppress mineralization and adhesion of the periodontal ligament at the time of tooth transplantation was not known in the art of record at the time of filing.

Given the lack of guidance in the specification describing any method of administering full-length human RGD-CAP *in vivo*, the absence of teachings in the specification that any amount of RGD-CAP administered by any means can contact periodontal ligament cells and induce changes in the cells similar to the observations made *in vitro* and that even if such changes were induced that this would suppress mineralization and adhesion of the implanted tooth, and the lack of teachings in the art that full-length human RGD-CAP can be used during tooth transplantation to suppress mineralization and adhesion in the periodontal ligament, the skilled artisan would be unable to practice the invention, except as a method of suppressing mineralization in periodontal ligament cells isolated from a human and cultured with a human

RGD-CAP protein, comprising SEQ ID NO:2, *in vitro*, without extensive and arduous experimentation.

Response to Arguments

Applicant's arguments filed 3/29/05 have been fully considered but they are not persuasive. Applicant argues that the examiner has not presented evidence demonstrating that one skilled in the art would doubt that RGD-CAP would suppress mineralization and adhesion in a patient. Further, applicant argues that the specification presents significant evidence supporting the asserted utility. This is not considered persuasive. Applicant should note that this not a utility rejection, it is an enablement rejection in which the asserted utility is not enabled. As described above the specification only presents data from *in vitro* experiments with cultured periodontal ligament cells. While the specification enables a method of suppressing mineralization in these cells *in vitro*, it does not enable the claimed *in vivo* method. This is due to the lack of correlation of the *in vitro* results observed with the claimed *in vivo* method.

Next applicant argues that there is significant evidence presented in the specification that demonstrates the function of RGD-CAP in the suppression of mineralization and adhesion. "Specifically, the examples demonstrated that RGD-CAP is expressed in the periodontal ligament (PDL, see pages 23-24); and RGD-CAP negatively effects alkaline phosphatase activity in PDL cells. However, as stated on page 24, this by itself; was not entirely determinative of the ability of RGD-CAP to suppress mineralization. For this, the applicants performed additional experiments, which demonstrated that additional mineralization markers were negatively effected (e.g., type 1 collagen and sialoprotein mRNAs-see page 25 and Fig. 3B) and also

decreased in alizarin red staining and bone nodule formation (see page 25 and Fig. 3C)." While these points are acknowledged, they do not address the core of the rejection, which is the lack of correlation between the *in vitro* results observed with the claimed *in vivo* method.

Applicant argues that *in vitro* tissue culture cells have substantially the same metabolic and physiological characteristics as cells present in a whole organism and, as such are often used to predict efficacy *in vivo.* It is not disputed that RGD-CAP is capable of inducing the same changes to periodontal ligament cells *in vivo* as *in vitro*. What has not been demonstrated in the specification is that: 1) this can be induced by any means of administration of RGD-CAP in any amount; and 2) that if said changes in mineralization markers in the periodontal cells are induced this will suppress mineralization and adhesion of the transplanted tooth.

Finally, applicant cites the reference of Kim et al., arguing that it provides evidence that *in vitro* experiments correlate with an *in vivo* effect. Kim et al. provides several experiments that show that RGD-CAP can suppress bone nodule formation *in vitro*. However, while these results support the *in vitro* results observed in the specification they do not provide insight into whether administering RGD-CAP to the periodontal ligament of teeth prior to administration will predictably induce changes that will suppress mineralization and adhesion.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of original claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention, is withdrawn. Applicant's cancellation of claim 4 filed 3/29/2005 have been fully considered and were found persuasive in overcoming the remaining grounds of rejection.

Claim Rejections - 35 USC § 102

The rejection of original claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Skonier et al. {Skonier et al. (1992) DNA Cell Biol. 1992 Sep; 11:511-22} is withdrawn. Applicant's cancellation of claim 4 filed 3/29/2005 have been fully considered and were found persuasive in overcoming the remaining grounds of rejection.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Lou Lieto whose telephone number is (571) 272-2932. The examiner can normally be reached on Monday-Friday, 9am-5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571)-272-0735. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Patent applicants with problems or questions regarding electronic images that can be viewed in the PAIR can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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